REMARKS

Claims 1 and 11 to 16 are present for purposes of prosecution.

Claims 4 to 10 have been withdrawn.

Applicants' invention as defined in independent Claim 1 is directed to a pharmaceutical composition which is a single dosage formulation in the form of a tablet containing metformin and glipizide which formulation contains 2 to 3% moisture, and including an outer protective coat or finishing layer surrounding the tablet, the formulation being designed to control moisture so that the glipizide does not hydrolyze and the metformin is compressible. Applicants' formulation as claimed is devoid of an enteric coating. The claimed formulation is therefore an immediate release formulation. It cannot be a sustained or controlled release formulation without an enteric coating.

The outer protective coating or finishing layer is not an enteric coating and will not serve to control release of the metformin and/or glipizide but only serves to protect the tablet from physical abrasion and prevent contact of the drug with liquids which cause premature dissolution and release of drug before it is ingested or before it is swallowed. The outer protective coating acts as a barrier against moisture and will minimize hydrolysis of the glipizide. See Example 1, page 26, lines 19 to 26 of the Specification.

Claim 11 which depends from Claim 1 defines the tablet as including a dosage of metformin of from about 250 to about 2500 mg/day and a dosage of glipizide from about 1.25 to about 25 mg/day.

Claim 12 which depends from Claim 1 defines the tablet as including metformin in a weight ratio to the glipizide of from about 1000:1 to about 100:1.

Claim 13 which depends from Claim 1 defines the tablet as including a dosage of metformin of 250 mg and the dosage of glipizide of 1.25 mg.

Claim 14 which depends from Claim 1 defines the tablet as including a dosage of metformin of 250 mg and a dosage of glipizide of 2.5 mg.

Claim 15 which depends from Claim 1 defines the tablet as including a dosage of metformin of 500 mg and a dosage of glipizide of 2.5 mg.

Claim 16 which depends from Claim 1 defines the tablet as including a dosage of metformin of 500 mg and a dosage of glipizide of 5 mg.

In the Final Rejection mailed July 14, 2004, the Examiner contends that

> "Claim 3 fails to further limit the subject matter of the claim 1 in which claim 3 ultimately depends upon. The newly amended claim 1 contains a negative provisio, 'said composition being devoid of an enteric coating'. In other words, the claimed composition excludes any possibility of having 'enteric coating' on the outer surface

> of the single dosage formulation (e.g., tablet). However, applicants' recitation of 'an outer protective coating or finishing layer surrounding said tablet' in claim 3 broadens out the scope of the claim 1 rather than further limiting the subject matter of the claim 1. The scope of 'an outer protective coating or finishing layer surrounding said tablet' encompasses 'enteric coating' as well as other types of coating techniques (e.g., seal coating, film coatings, barrier coatings, compress coatings, fast disintegrating coatings, or enzyme degradable coatings) that are known in the arts. This inconsistency leaves the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear."

Claim 3 is now merged into amended Claim 1.

Applicants agree with the Examiner that Claim 1 which includes the proviso " ' said composition being devoid of an enteric coating' . . . excludes any possibility of having an 'enteric coating' on the outer surface of the single dosage formulation (e.g. tablet)."

The "outer protective coating or finishing layer surrounding said tablet" defined in Claim 1 is not an enteric coating and does not encompass an enteric coating. How can it? Claim 1 defines the composition as being devoid of an enteric coating. Thus, the outer protective coating or finishing layer must be other than an enteric coating.

In Applicants' Specification at page 16, starting at line 25, "enteric coated glipizide particles" are disclosed. It is also indicated that the enteric coated glipizide particles "may be further coated with an outer protective finishing coat or layer . . . ." Applicants would not coat enteric coated particles with an enteric coating. The protective finishing coat or layer is exactly that, a protective coat and not an enteric coat. Applicants' protective finishing coat or layer protects the composition from physical abrasion or premature contact with liquids or other materials which could possibly cause premature release of the drug. The protective finishing coating or layer functions to delay release of the drug before the dosage form is ingested or swallowed. Once swallowed, the protective coat does <u>not</u> delay or control release of drug in the body. It is the enteric coat which controls release of the drug in the body.

Protective finishing coat or layer is not encompassed by "enteric coat".

Accordingly, it is clear that Claim 3 does limit the subject matter of Claims 2 and 1, into which Claim 3 has been merged. Thus, it is submitted that the Examiner's objection to Claim 3 (now merged into Claim 1) should be withdrawn.

Claims 1 to 3 and 11 to 16 are rejected under 35 U.S.C. §103(a) as being unpatentable over Chen et al. (U.S. 6,099,862) in view of Patel et al. (U.S. 6,248,363 B1).

The Examiner contends that:

> "Chen teaches a pharmaceutical tablet containing a combination of metformin and glipizide, wherein core of said composition is prepared by mixing metformin and

glipizide with povidone, sodium lauryl sulfate and magnesium stearate and then tablet is optionally seal coated with an opadry materals. As specific embodiments of the claimed invention, Examples (1-2) discloses 850mg or 500mg of metformin HCl and 5 mg of glipizide controlled release tablet, wherein granules containing metformin and glipizide are dried 'in the fluidized bed coater until the loss on drying is less than 2%' and then compressed to tablet. However, Chen is silent about the claimed 'being devoid of an enteric coating'; '2 to 3% by weight moisture'; and the specific dosage amounts of metformin and glipizide in said composition.

However, it would have been obvious in view of Patel (U.S. 6,248,363 B1) who teaches pharmaceutical delivery systems for pharmaceutical active ingredients including metformin and glipizide, wherein said active ingredients can be prepared in various dosage forms (e.g., tablet, capsule, quick or fast dissolving tablet, granule, etc. . .); coated with various coating methods (e.g., enteric coating, seal coating, protected coating or layered coating, etc. . .). . . .

With respect to the instantly required 'devoid of an enteric coating', Patel teaches that determination of appropriate dosage forms (e.g., tablet covered with enteric coating or with protective coating or finishing layer) having optimum therapeutic index is well considered within the skill of the artisan, and the artisan would be motivated to determine optimum dosage forms to maximize the effects of the drug. Therefore, the references in combination make obvious the claimed invention.

With respect to the 'from 2 to 3% by weight moisture', the prior art does not disclose the instantly required moisture concentration. However, one having ordinary skill in the art would have expected at the time the invention was made that the weight moisture would have been characteristic of the modified prior art method. Generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art there is evidence indicating such concentration is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

* * *

The above references in combination make clear that the combination of metformin and glipizide in single dosage formulation is old and well known in the art. The above references in combination also make clear that the preparation of pharmaceutical composition containing metformin and/or glipizide in various dosage forms (e.g., tablet, quick, fast dissolving tablet, capsule, etc. . .) coated with coating techniques (e.g., enteric coating, protective coating, seal coating, etc. . .) designed for various dosage form release systems (e.g., immediate release, controlled release, delayed release, etc. . .) is old and well known in the art. One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a)."

It is submitted that Applicants' composition as claimed is patentable over U.S. Patent No. 6,099,862 to Chen et al.

Chen et al. disclose a controlled release tablet which, as disclosed in Example 1, may include a combination of metformin HCl (800 mg) and glipizide (5 mg) in a tablet core and as disclosed in Example 2, may include a combination of metformin HCl (500 mg) and glipizide (5 mg) in a tablet core. The Chen et al. Examples 1 and 2 tablet cores include a seal coating and a sustained release coating formed of a semi-permeable membrane which is formed of cellulose acetate, triacetin (plasticizer) and PEG400. The sustained release coating includes one hole drilled onto each side of the sustained release tablet, which holes allow for release of drugs.

The tablet cores of Examples 1 and 2 of Chen et al. are formed by a granulation technique where granules containing metformin and glipizide "are dried in the fluidized bed coater until the loss on drying is less than 2%."

After the seal coating and sustained release semi-permeable membrane coating are applied by Chen et al., the coated tablets are dried before the holes are drilled into the sustained release tablets.

If it is submitted that Applicants' composition as claimed in Claims 1 to 3 and 11 to 16 are patentable over Chen et al. As indicated, in Claim 1, Applicants' tablets are devoid of an enteric coating and therefore are immediate release tablets. The Chen et al. tablets contain an enteric coat or layer which is a semi-permeable membrane and thus are sustained release tablets, which as shown in Examples 1 and 2 release drugs over a 16 hour period.

In addition, Applicants' tablets must include sufficient moisture (2 to 3%) to leave the metformin sufficiently compressible so that tablets may be formed. However, the water content must not be greater than 3% to ensure that the glipizide will not be hydrolyzed.

There is no disclosure or suggestion in Chen et al. of an immediate release composition or tablet (devoid of an enteric coat) as claimed herein.

There is no disclosure or suggestion in Chen et al. of an immediate release composition or tablet (devoid of an enteric coat) that contains 2 to 3% moisture.

There is nothing in Chen et al. which would motivate one skilled in the art to change the Chen et al. tablet to redesign the sustained release tablet with a semi-permeable membrane which includes openings in the tablet to allow drugs to be released to form an immediate release tablet which is devoid of an enteric coating.

The differences between Applicants' invention as claimed and the tablet of Chen et al. are significant and unobvious so that the subject matter of Applicants' invention as a whole would not be obvious to one skilled in the art.

For the aforementioned reasons, it is submitted that Applicants' invention as claimed in Claims 1 and 11 to 16 is patentable over Chen et al.

It is submitted that Applicants' invention as claimed in Claims 1 to 3 and 11 to 16 is patentable over U.S. Patent No. 6,248,363 to Patel et al.

Patel et al. disclose solid pharmaceutical compositions which include a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate, the encapsulation coat including at least one ionic or non-ionic hydrophilic surfactant and/or a lipophilic surfactant or a triglyceride, and a pharmaceutical active component. Other similar embodiments are disclosed as well, all of which much include an encapsulation coat which will contain the pharmaceutical active ingredient.

There is no disclosure or suggestion in Patel et al. of a tablet which includes a combination of metformin and glipizide. In addition, there is no disclosure or suggestion in Patel et al. of a tablet which must be prepared in a manner to include 2 to 3% moisture to leave the metformin sufficiently compressible so that tablets may be formed while ensuring that the water content is not greater than 3% so that the glipizide (employed in combination with the metformin) will not hydrolyze.

Furthermore, Patel et al. include their pharmaceutical active ingredient in the encapsulation coat while Applicants employ the metformin and glipizide in the tablet core.

For the above reasons, it is clear that Applicants' composition as claimed is patentable over Patel et al.

It is also submitted that Applicants' invention as claimed is patentable over a combination of Chen et al. taken with Patel et al.

Chen et al. teaches a sustained release tablet which contains a combination of metformin and glipizide in a tablet core which is coated with a seal coating and a sustained release coating. Applicants' composition includes the seal coating but does not include the sustained release coating since Applicants' composition is not a sustained release composition. The Chen et al. tablets include less than 2% moisture whereas Applicants' composition must include at least 2% moisture but no more than 3% moisture. Thus, Chen et al. is totally devoid of Applicants' inventive concept as defined in Claim 1, that is a pharmaceutical composition which does not include a sustained release coating and which includes from 2 to 3% moisture which allows the metformin to be compressible to enable tablet formation but which will not cause hydrolysis of the glipizide. The above differences are material and unobvious. Patel et al. adds nothing to Chen et al. which would make Applicants' composition obvious. Patel et al. does not disclose a pharmaceutical composition containing a combination of metformin and glipizide. Patel et al. does not address the moisture problem employing metformin and glipizide in a single formulation and its solution. Patel et al. disclose employing an encapsulation coat which will contain the active component whereas Applicants employ the metformin and glipizide in the tablet core. A combination of Chen et al. and

Patel et al. would merely suggest to or motivate one skilled in the art to include a drug in the enteric coating of Chen et al. and do nothing about moisture content or to modify. At best the rejection of the claims is based on modifying the Chen et al. enteric coated sustained release tablet, using hindsight in view of Applicants' disclosure, so as to completely change its basic nature to omit the enteric coating and turn it into an immediate release tablet. The latter would, of course, be improper as lacking any foundation, in fact. There is nothing in either Chen et al. or Patel et al. that would suggest that Chen et al. should be so modified. Thus, it is submitted that Applicants' invention as claimed is patentable over the combination of Chen et al. taken in view of Patel et al.

It is also submitted that there is no disclosure or suggestion in either of the cited references or combination thereof of the composition claimed in Claims 1 to 3 and 11 to 16. Absent the use of hindsight in view of Applicants' disclosure, there would be no reason for one skilled in the art reading the cited references to combine these references. The use of hindsight in view of Applicants' disclosure in combining references to reject Applicants' claims is clearly improper in view of In re Pye et al., 148 U.S.P.Q. 426 (CCPA 1966), ACS Hospital Systems, Inc. v. Montefiore Hospital, supra.; and W.L. Gore & Assoc., Inc. v. Garlock, Inc.., supra.

In view of the foregoing, it is believed that Claims 1 and 11 to 16 overcome all formal objections and are patentable over the cited combination of references. Accordingly, it is believed that Claims 1 and 11 to 16 are in condition for allowance.

Respectfully submitted,

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